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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HAYES, ROBERT CLINTON

ART UNIT PAPER NUMBER

1647

DATE MAILED: 05/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/423,516

Applicant(s)

GHERARDI ET AL.

Examiner

Robert C. Hayes, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 January 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 64-86 is/are pending in the application.
- 4a) Of the above claim(s) 80-86 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 64-79 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 64-86 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/28/05</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Arguments

1. The amendment filed on 1/28/05 has been entered.
2. It is noted that the Examiner's suggestion to amend the claims to recite that the wildtype human HGF is of SEQ ID NO: 2, which should have obviated most of the rejections made of record, was again ignored by Applicants.
3. Applicant's arguments filed 1/28/05 have already been fully considered, but were not deemed to be persuasive.
4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
5. Claims 64-79 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reason made of record in Paper NOs: 18 (mailed 6/27/02), 24 (mailed 1/09/04) & 20040805, and as follows.

It is noted that Applicants fail to clearly separate and argue each rejection individually. It appears that pages 5-7 of the response attempts to argue that various WIPO and US patents

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describe “additional mutations” in “variant HGF molecules”. In contrast, this a written description rejection where the *claimed* invention only recites an incomplete starting point of a “hairpin loop structure” of SEQ ID NO: 3 that is then modified. No structurally known and definable complete and functional HGF molecules are described in the claims. No variant/genus HGF molecules are adequately described in the claims, whose structure can be ascertained. In contrast, a human wildtype base structure HGF molecule of SEQ ID NO: 2 can be defined, as well as variants thereof within the recited hairpin loop structure, which then possess the recited functional limitations. In contrast, Applicants have ignored the Examiner’s suggestion to amend the claims accordingly. Additionally, no appropriate functional and structural limitations are currently recited for any other variant HGF molecule that would reasonably meet the written description requirements previously made of record, consistent with that held by the courts in *Fiers v. Revel* and *Univ. California v. Eli Lilly and Co.* previously made of record, which further are not adequately described on pages 9-12 of the specification, and in which only open-ended definitions of putative “variant HGF molecules” are disclosed, in contrast to Applicants’ assertions on page 4, etc. of the response. Thus, Applicants’ arguments are not on point in regards to this particular rejection. However, Applicants are correct that *Fiddes v. Baird* no longer applies, based on the previous amendment of the claims.

In summary, base claim 64 still recites insufficient structure, because SEQ ID NO: 2 is the wildtype sequence of 728 amino acid residues, but SEQ ID NO: 3 is merely an 27 amino acid fragment, **which does not represent wild-type human HGF**, and therefore, remains not limited to a variant that merely replaces a positively charged amino acid residue in the hairpin loop structure of **wildtype** human HGF, as argued by Applicants; thereby, still not meeting the written

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description guidelines for the reasons extensively made of record; consistent with that held by the courts in *Fiers v. Revel* and *Univ. California v. Eli Lilly and Co.*, previously made of record. Nor are the **claims** limited to any definable “hairpin substitution”, such as “D117, E159, R197, V692, R73, in a *complete and structurally definable HGF* molecule. Thus, Applicants’ arguments are not persuasive. See again MPEP 2163.

6. Claims 64-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons made of record on Paper No: 20040805.

Applicants argue on page 7 of the response that “[p]age 9, lines 7-9, for example, states that in addition to the positive to negative-charged hairpin loop mutations, the same HGF molecules [of SEQ ID NO: 2] may be modified further”. In contrast to Applicants’ assertions, Applicants are mixing and matching the different concepts of a fragment of SEQ ID NO: 2 (i.e., SEQ ID NO: 3) and amino acid substitutions to SEQ ID NO: 2; thereby, constituting new matter. Note further that a “hairpin loop structure [of SEQ ID NO: 3]” does not identify a “wild-type human HGF”.

In summary, no proper basis nor conception in context with that described within the specification exists for inserting the hairpin structure of SEQ ID NO: 3 into any different “wild-type human HGF” molecule, except for the human wild-type HGF molecule of SEQ ID NO: 2; thereby, broadening the scope of that claimed, and thereby, constituting new matter.

7. Claims 64-79 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to HGF variants that are structurally characterized and claimed, does not reasonably provide enablement for any biologically functional equivalent forms of HGF with no recited structural characteristics. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reason made of record in Paper No: 18 (mailed 6/27/02), 24 (mailed 1/09/04) & 20040805, and as follows.

Applicants argue on pages 1-3 & 7-9 that “[t]he Rudinger reference is however submitted to be misleading in the context of the claimed invention [because] “as of May 1997, the conclusions of Rudinger were over twenty years out-of-date, and the science of protein engineering had significantly advanced since 1976”. Applicants then argue that “as of the priority date of this application, May 1997, it was well known in the field of protein engineering that the majority of replacement mutations in a protein have little or no effect on protein folding, stability or activity, and that amino acid substitution at selected sites are required in order to change protein activity”, and cites the teachings of Gassner et al. (1996), Huang et al. (1996), Rennell et al. (1991), Bowie et al. (1990) and Axe et al. (1996). In contrast to Applicants’ assertions, the claims are not limited to “replacement mutations” or to “amino acid substitution at selected sites” in any structurally defined/claimed protein, as previously made of record. Moreover, Applicants’ assertion that as of “May 1997 it was well known in the field of protein engineering that the majority of replacement mutations in a protein have little or no effect on

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protein folding, stability or activity” is not supported by the references cited. In contrast, Gassner et al teach that “*it is possible*, however, that a *limited number* of combination of amino acids *are viable*, and that they are the ones identified by the mutagenic selection...[where] there is no selection other than the sites of substitution” using T4 bacteriophage (pg. 12155, 1st col). Huang et al teach “among functional [*E. coli*] β -lactamase mutants with *conserved residues* in the β -lactamase gene family identified *many positions which did not tolerate substitutions...*” [emphasis added](Abstract). Rennell et al teach that “[t]he effects of many of the deleterious substitutions are interpreted in light of the known [crystallographically] structure of T4 [bacteriophage] lysozyme”, but the “relative contributions to biological function of many residues in the molecule are unknown” (Abstract & pg. 67, 2nd col), and in which the crystalline structure of HGF of the instant invention is unknown and not described. Bowie et al. further teach that “it should be possible to predict structure from sequence, and subsequently to infer detailed aspects to an exact manner from the structure. However, both problems are *extremely complex*, and *it seems unlikely* that either will be *solved* in an exact manner *in the near future* [emphasis added]” (Abstract). And Axe et al then teach, in contrast to Applicants’ assertions, that “[i]ntroduction of even small changes to a hydrophobic core typically diminishes the packing quality, *the stability*, and (often) *the activity of the protein*” [emphasis added]. In other words, all of these references alternatively support the rejection made of record and the teachings of Rudinger, which therefore is not out-of-date, by definition. Moreover, Rudinger is still appropriate because human HGF is a hormone, like the peptide hormones illustrated by Rudinger, and where eukaryotic proteins have similar properties and considerations, which are different from bacterial β -lactamase, or bacteriophages, used in the references cited by

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Applicants. Nevertheless, in contrast to Applicants' assertion that Rudinger is "misleading", the court held in *In re Wright*, 193 USPQ 332 (CCPA 1997), that the age of a reference is immaterial, absent subsequent evidence contradicting its teachings, which Applicants have clearly failed to provide, as discussed above, and which alternatively confirm the teachings of Rudinger, albeit in bacterial systems.

Lastly, it is noted that each case is decided on its own merits. Therefore, what other U.S. Patents claim are immaterial to the issues examined in the instant application; especially when the fact situations are never identical in one case to the other. Applicants' comments are therefore not on point, and inappropriate regarding the "validity of a U.S. Patent".

In summary, as previously made of record, no base structure for what constitutes the complete wildtype HGF from which the variant HGF molecule is derived is defined in the currently recited claims. Thus, Applicants' arguments remain moot, for the reasons previously made of record; consistent with the teachings of Rudinger previously made of record, and that held by the court in *Ex parte Maizel* previously made of record.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (571) 272-0885. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached on (571) 272-0961. The fax phone number for this Group is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert C. Hayes, Ph.D.
May 6, 2005

ROBERT C. HAYES, PH.D.
PATENT EXAMINER